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ORIGINAL RESEARCH

Positive impact on 10-year outcome of the window of opportunity for conventional synthetic DMARDs in rheumatoid arthritis: results from the ESPOIR cohort

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ABSTRACT

Objective This study aimed to assess the impact of disease-modifying antirheumatic drugs (DMARDs) on 10-year outcomes in rheumatoid arthritis (RA).

Methods Patients with RA from the ESPOIR cohort with complete data on Disease Activity Score in 28 Joints (DAS28) and Health Assessment Questionnaire (HAQ) at 10 years (n=418) and complete radiographic data at baseline and 10 years (n=343) were included in this study. Outcomes were favourable outcome (FavOut) at 10 years, defined as DAS28 of <2.6 and HAQ score of <0.5 at 10 years, and absence of structural damage progression (AbsSDP) at 10 years, defined as change in Sharp-van der Heijde Score less than the smallest detectable change at 10 years (11.5 points). Three multivariate logistic regression models predicting 10-year outcome were built, considering (1) baseline variables only, (2) baseline variables and DMARD exposure (ever exposed, yes/no) and (3) baseline variables and DMARD exposure as weighted cumulative exposure (WCE) variables.

Results Overall, 196/418 (46.9%) patients showed FavOut and 252/343 (73.5%) AbsSDP. WCE models had the best predictive performance, with area under the curve=0.80 (95% CI 0.74 to 0.87) for FavOut and 0.87 (95% CI 0.83 to 0.92) for AbsSDP. In the WCE model, the odds of FavOut and AbsSDP were reduced with conventional synthetic disease-modifying antirheumatic drug (csDMARD) initiation at 12 months versus at baseline (OR 0.78, 95% CI 0.65 to 0.94, and OR 0.89, 95% CI 0.76 to 0.98, respectively). Early biologics initiation was not significantly associated with either outcome.

Conclusions WCE models can identify and quantify the long-term benefit of early csDMARD initiation on 10-year functional and structural outcomes in patients with RA.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ The concept of a window of opportunity (WoO) in rheumatoid arthritis (RA) has mostly been demonstrated with short-term outcomes in randomised controlled trials.

⇒ In observational studies, modelling accurately the exposure to treatments remains an important issue.

WHAT DOES THIS STUDY ADD?

⇒ This study is the first to use weighted cumulative exposure (WCE) method, which takes into account the dosage and duration of exposure to treatments, to assess the impact of treatments on RA 10-year outcomes.

⇒ In this study, WCE models identified and quantified the long-term benefit of early conventional synthetic disease-modifying antirheumatic drug initiation (DMARD) on 10-year functional and structural outcomes in patients with RA.

HOW MIGHT THIS IMPACT ON CLINICAL PRACTICE OR FURTHER DEVELOPMENTS?

⇒ These results confirm the long-term beneficial consequences associated with respect to a 3-month WoO when starting a DMARD in patients with early RA, and highlight the need to properly take into account treatment exposure, in terms of intensity and duration, to assess the potential long-term benefits in RA.

INTRODUCTION

Recent therapeutic strategies have revolutionised the prognosis of patients with rheumatoid arthritis (RA).[1] This formerly debilitating and disabling disease[2] is today considered sustainably maintained in remission, and both joint erosions and dislocations can be largely avoided, which results in reduced rate of surgical joint replacement and preservation of quality of life.[3] This situation can be explained first by a more accurate and rapid diagnosis which, combined with early drug initiation, prevents progression of joint damage in 90% of patients with early RA.[4] A

second important factor is therapeutic innovation, with an increasing number of molecules available to treat RA. Indeed, therapeutic management has greatly improved with the development of biological disease-modifying antirheumatic drugs (bDMARDs),[1] which has allowed for better disease activity control in patients responding insufficiently to conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). The third factor is tight control and treat-to-target strategies. Thus, the most recent recommendations of the EULAR and the American College of Rheumatology (ACR) promote a strategic approach to achieve low disease activity or remission in routine clinical practice, to maximise long-term health benefits, to control joint destruction and to prevent disability.[5 6] According to these recommendations, csDMARDs should be used as first-line treatment, whereas bDMARDs should be combined with csDMARDs in patients showing inadequate response to csDMARDs.[5 6]

Furthermore, several studies suggested the benefit of early initiation of disease-modifying antirheumatic drugs (DMARDs) (particularly csDMARDs) to prevent the occurrence of unfavourable outcomes, such as functional disability, pain, joint involvement and structural damage progression (SDP)[7 8]; however, this concept of a window of opportunity (WoO) has mostly been demonstrated with rather short-term outcomes in randomised controlled trials. To estimate the long-term benefits of WoO, we need to disentangle the potential benefit of the WoO from the RA natural evolution and the consequences of therapies used over the years, respectively, taking into account the potential confounders that lead to patients with the most severe disease likely receiving the most recent and efficacious therapies.

Recently, a statistical method was developed to model cumulative drug exposure and its effect on the risk of an event: the weighted cumulative exposure (WCE) method.[9] In this method, drug exposure is considered a weighted sum of past doses. Only a few studies have applied this method in rheumatology, but some showed that glucocorticoids do increase the risk of serious infections over time, and especially recent intakes.[10]

The aim of the present study was to use the WCE approach to assess the long-term impact (10 years) of actual therapeutic strategies implemented in RA.

METHODS

Study design

The Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) cohort is a French multicentre cohort following patients with early RA at the time of inclusion. The full protocol of the ESPOIR cohort has been described elsewhere.[11] In brief, adult patients with at least two swollen joints for more than 6 weeks but less than 6 months, a suspected or confirmed diagnosis of RA, and no intake of glucocorticoids and DMARDs for more than 2 weeks were included between January 2003 and March 2005 and followed up prospectively once or twice a year for more than 10 years. The main exclusion criterion was the presence of another clearly defined inflammatory rheumatic disease.

In the present study, patients from the ESPOIR cohort were considered if they fulfilled ACR/EULAR 2010 criteria at least once during the follow-up,[12] if they had complete disease activity and functional capacity data at 10 years and if they had complete radiographic data at baseline and 10 years.

The therapeutic strategy was left to the choice of each patient's rheumatologist and was not predefined in the cohort protocol.

Patients were followed up every 6 months for the 2 first years, then every year for the 8 remaining years. At each visit, a set of clinical and biological variables was recorded, including comorbidities, treatments, details from the rheumatological physical examination, evaluation of disease activity by Disease Activity Score in 28 Joints (DAS28), assessment of functional capacities by the Health Assessment Questionnaire Disability Index (HAQ-DI), erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) levels. Radiographic data were from hands and feet radiographs, which were obtained five times during follow-up: baseline (month 0) and 2, 5, 7 and 10 years. Radiographs were analysed by two experienced readers, in chronological order, with blinding to patients' identity and data.[13] The modified Sharp-van der Heijde Score (vSHS) was calculated to assess SDP.[14]

Outcomes

Two major outcomes were studied independently in the present work. The first was favourable outcome (FavOut) at 10 years, defined as DAS28-ESR of <2.6 and HAQ-DI of <0.5 at 10 years.[15] The second outcome was the absence of structural damage progression (AbsSDP) at 10 years, defined as a change in vSHS below the smallest detectable change at 10 years[16]; in the present study, the smallest detectable change at 10 years was 11.5 points.[16]

Predictors

Baseline characteristics were considered potential predictors of FavOut and AbsSDP at 10 years. These characteristics were sociodemographic (age, sex, personal income and low income being defined as <610 €/month), clinical (joint involvement, extra-articular symptoms, comorbidities, DAS28, HAQ-DI, patient global assessment and fatigue assessment), biological (autoantibodies and acute phase reactants) and radiographic (vSHS and presence of typical erosions) variables found associated with RA outcomes in previous studies, including matrix studies based on the ESPOIR cohort.[17 18]

Treatments of interest

Information regarding treatment was collected at each visit, including initiation and (if applicable) discontinuation dates, posology, and frequency and route of administration. In the present study, the treatments considered were (1) csDMARDs: methotrexate, sulfasalazine

and leflunomide and (2) bDMARDs: tumour necrosis factor blockers (adalimumab, etanercept, certolizumab, golimumab and infliximab), rituximab, tocilizumab and abatacept. Hydroxychloroquine was not considered, given that it did not show any effect on SDP in RA.[19]

Posologies of csDMARDs and bDMARDs were standardised by dose quotient (DoseQ; ie, the ratio between the received dose and the recommended dose for each drug) (online supplemental material 1).[20]

Analyses were also adjusted on oral glucocorticoid intake, with dosages standardised by prednisone equivalent.

Statistical analysis

Patients and baseline characteristics are described with means (SD) for quantitative variables and number (%) for qualitative variables.

Drug exposure models

First, each drug exposure (csDMARDs or bDMARDs) was presented as a binary indicator variable (ever-treated, yes or no).

Second, each drug exposure was represented as the weighted sum of past doses by the WCE variable. Because pharmacokinetics and pharmacodynamics characteristics of treatments are rarely known, Abrahamowicz *et al*[21–23] developed a flexible WCE model approach in which the weight function is estimated from the available data with cubic regression B-splines. Because of the uncertainty in support intervals and number of B-splines, WCE variables with a variable number of knots (one to six) and spline degree of 1° or 3° were fitted, and the best set of parameters was chosen based on the Akaike Information Criterion (AIC).

Modelling drug exposure as WCE variables allows for comparing deferent 'profiles' of drug intake (ie, different dosages, different duration of treatment exposure or both). In the present study, we considered a fixed posology of 1 DoseQ for both csDMARDs and bDMARDs, a time window of 10 years and tested different durations of exposure for each treatment category (figure 1).

Predictive models for 10-year outcomes

Three multivariate logistic regression models aiming to predict FavOut or AbsSDP at 10 years were built and compared.

The first model included only clinical, biological and radiological characteristics at baseline ('baseline model' (BSL)). Quantitative variables were compared by Student t-test or Mann-Whitney test, and categorical variables were compared by χ^2 test or Fisher exact test. Variables with p values of <0.2 on univariate analysis were included in a multivariable stepwise regression analysis with backward elimination based on the AIC to build the final multivariate BSL.

A second model ('binary treatment model' (BIT)) was built with previously selected baseline characteristics and

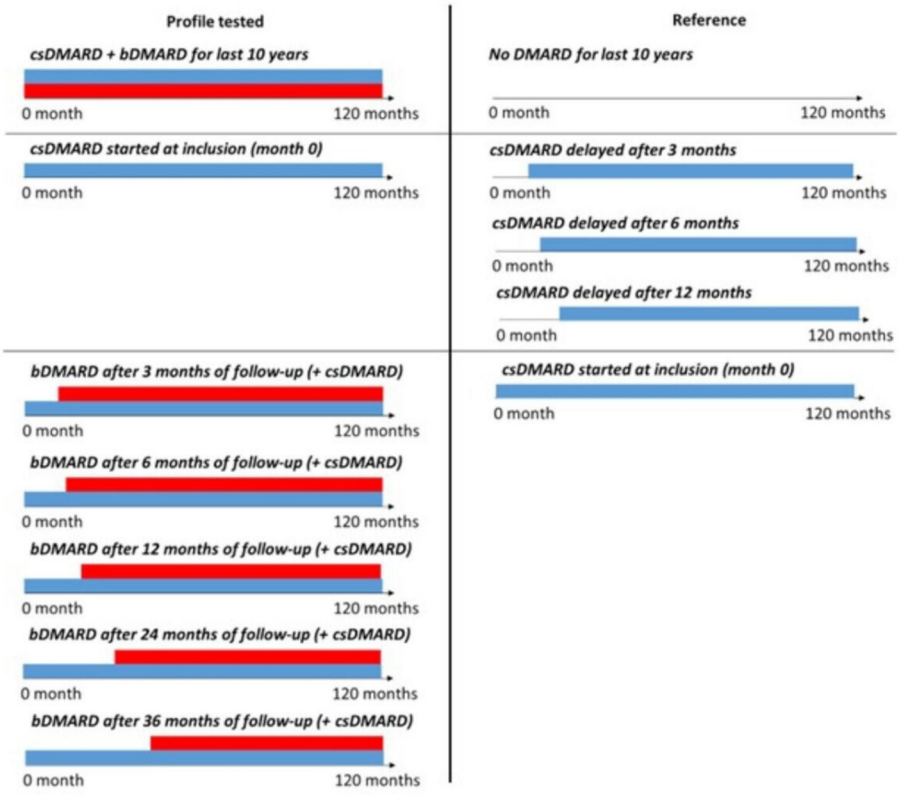


Figure 1 Comparison of profiles of treatment intake in the weighted cumulative exposure combined models. bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug.

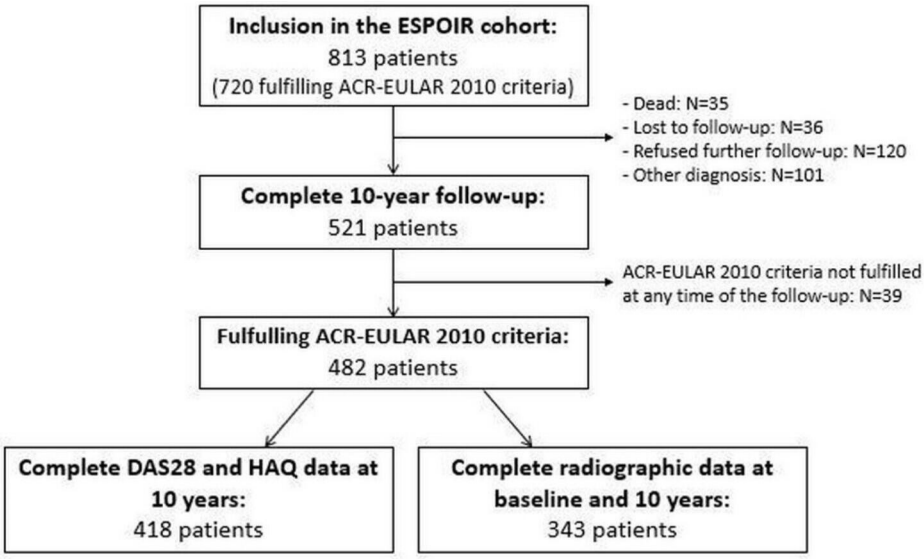


Figure 2 Flowchart of participants in the study. ACR, American College of Rheumatology; DAS28, Disease Activity Score in 28 Joints; ESPOUR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; HAQ, Health Assessment Questionnaire.

treatment variables considered as simple binary variables (treated, yes/no at any time during follow-up).

Finally, a model including previously selected baseline characteristics and treatments as WCE variables was built ('WCE combined model'). Significant WCE variables from univariate analysis were considered for multivariable analysis. Then, multivariate models were built including each selected WCE variable and previously selected baseline characteristics; the WCE variables that remained significantly associated with 10-year outcomes were included in a final WCE combined model, considering several treatment exposures and previously selected baseline characteristics. Sensitivity analyses were also performed, considering in the WCE models patients having initiated a DMARD in the first year of follow-up.

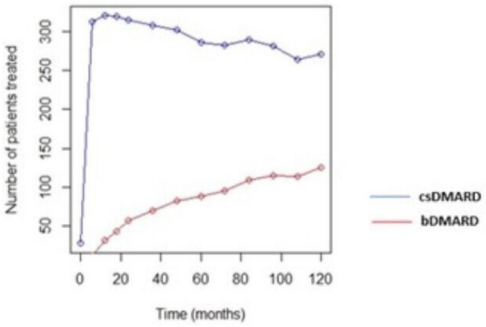
The performance of all models was evaluated and compared by receiver operating characteristic curve analysis and calculation of the area under the curve (AUC) and its 95% CI (computed with 2000 stratified bootstrap replicates). Statistical analyses involved using R V.3.3.1 (R

Table 1 Baseline characteristics of study groups

Variables	AbsSDP group (n=343)	FavOut group (n=418)	Overall ESPOIR cohort (n=813)
Age at RA onset (years)	48.8±11.4 (50.9)	48.3±11.6 (50.1)	48.1±12.6 (50.1)
Female sex	276 (80.5)	325 (77.8)	624 (76.8)
Smokers	158 (46.1)	198 (47.4)	388 (47.7)
TJC at baseline (/28)	9.2±7.2 (7.0)	8.8±7.1 (7.0)	8.4±7.0 (6.0)
SJC at baseline (/28)	8.1±5.4 (7.0)	7.8±5.4 (6.0)	7.2±5.4 (6.0)
Extra-articular involvement at baseline	198 (57.7)	233 (55.7)	444 (55.9)
DAS28-ESR at baseline	5.2±1.3 (5.1)	5.2±1.3 (5.1)	5.1±1.3 (5.1)
HAQ-DI at baseline	1.0±0.7 (0.9)	1.0±0.7 (0.9)	1.0±0.7 (0.9)
RF IgM-positive	186 (54.2)	237 (56.7)	372 (45.8)
ACPA-positive	170 (49.6)	220 (52.6)	315 (38.8)
ESR at baseline (mm at 1 hour)	29.0±25.2 (22.0)	29.4±25.3 (22.0)	29.4±24.6 (22.0)
CRP at baseline (mg/L)	20.0±29.7 (9.0)	21.9±35.0 (9.0)	22.2±33.6 (9.0)
Erosion at baseline	88 (25.7)	110 (26.3)	185 (25.1)
Total vSHS at baseline	2.9±4.9 (1.3)	2.7±4.7 (1.3)	2.8±5.0 (1.3)

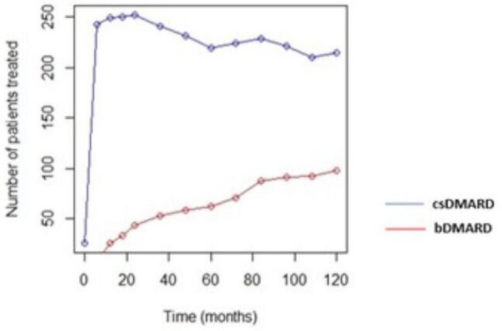
Data are means±SD (median), or n (%).
.AbsSDP, absence of structural damage progression; ACPA, anticitrullinated peptide antibody; CRP, C reactive protein; DAS28, Disease Activity Score in 28 Joints; ESPOIR, Etude et Suivi des Polyarthrites Indifférenciées Récentes; ESR, erythrocyte sedimentation rate; FavOut, favourable outcome; HAQ-DI, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis; RF, rheumatoid factor; SJC, swollen joint count; TJC, tender joint count; vSHS, Sharp-van der Heijde Score.

A



	M0	M6	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120
csDMARD	28 (6.7%)	312 (74.6%)	320 (76.6%)	319 (76.3%)	315 (75.4%)	308 (73.7%)	302 (72.3%)	286 (68.4%)	282 (67.4%)	289 (69.1%)	281 (67.2%)	264 (63.2%)	271 (64.8%)
bDMARD	0 (0.0%)	12 (2.9%)	32 (7.7%)	44 (10.5%)	57 (13.6%)	70 (16.8%)	83 (19.9%)	89 (21.3%)	96 (23.0%)	109 (26.1%)	152 (27.5%)	114 (27.3%)	125 (29.9%)

B



	M0	M6	M12	M18	M24	M36	M48	M60	M72	M84	M96	M108	M120
csDMARD	26 (7.6%)	243 (70.9%)	249 (72.6%)	250 (72.9%)	252 (73.5%)	241 (70.3%)	231 (67.4%)	219 (63.9%)	224 (65.3%)	229 (66.8%)	221 (64.4%)	210 (61.2%)	215 (62.7%)
bDMARD	0 (0.0%)	8 (2.3%)	26 (7.6%)	33 (9.6%)	44 (12.8%)	53 (15.5%)	59 (17.2%)	62 (18.1%)	71 (20.7%)	88 (25.7%)	91 (26.5%)	92 (26.8%)	98 (28.6%)

Figure 3 Exposure to treatments during the 10-year follow-up in the (A) favourable outcome group (n=418) and the (B) absence of structural damage progression group (n=343). bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug.

Foundation for Statistical Computing, Vienna, Austria). Significance was defined as a p value of <0.05.

The protocol of the ESPOIR cohort study was registered in ClinicalTrials.gov (NCT03666091).

RESULTS

Study population

Among the 813 patients included in the ESPOIR cohort, 720 fulfilled ACR/EULAR 2010 criteria at least once during the 10-year follow-up. At 10 years, 521 patients completed the follow-up, 482 of whom fulfilled ACR/EULAR 2010 criteria at least at one time point. Overall, 418 patients had complete DAS28-ESR and Health Assessment Questionnaire data at 10 years and were considered in the analysis of FavOut at 10 years, and 343 had complete radiographic data at baseline and 10 years and were considered in the analysis of AbsSDP at 10 years (figure 2).

Patients in the study groups were mostly female, with a mean age of 48 at RA onset (48.8±11.4 in the AbsSDP group and 48.3±11.6 in the FavOut group) and a mean DAS28 of 5.2±1.3 at inclusion in the ESPOIR cohort (table 1). Such patients did not differ from the overall ESPOIR cohort population except for rheumatoid factor and ACPA positivity, which was more frequent in the two study cohorts than in the overall ESPOIR cohort.

Treatment exposure

Description of csDMARD and bDMARD exposures in the two study groups and in patients not considered in the analyses is provided in online supplemental material 2 (see figure 3).

Overall, 374 (89.5%) and 300 (87.5%) patients in the FavOut and AbsSDP groups were exposed to csDMARDs during the 10-year follow-up, with a mean delay of initiation of 69.3 and 66.1 days since the start of the symptoms, respectively. The most prescribed csDMARD was methotrexate: 346 (82.8%) and 275 (80.2%) in the FavOut and AbsSDP groups.

bMARDs were used during the 10-year follow-up by 150 (35.9%) and 118 (34.4%) patients in the FavOut and AbsSDP groups, with a mean delay of initiation of

Table 2 Results from the BSL and BIT for FavOut and AbsSDP

	BSL for FavOut					BIT for FavOut
	Univariate analysis				Multivariable analysis	Multivariable analysis
Variables	No FavOut (n=222)	FavOut (n=196)	OR for FavOut (95% CI)	P value	OR for FavOut (95% CI)	OR for FavOut (95% CI)
Age (years)	50.3 (11.2)	46.0 (11.6)	0.97 (0.95 to 0.98)	0.0001	0.96 (0.94 to 0.98)	0.95 (0.92 to 0.97)
HAQ-DI	1.1 (0.7)	0.9 (0.6)	0.60 (0.45 to 0.81)	<0.0001	0.65 (0.42 to 1.02)	0.67 (0.42 to 1.07)
DAS28-ESR	5.3 (1.2)	5.0 (1.4)	0.84 (0.73 to 0.98)	0.03	1.25 (0.96 to 1.59)	1.34 (1.03 to 1.75)
Mean total vSHS	3.3 (5.2)	2.1 (4.1)	0.94 (0.89 to 0.99)	0.02	0.96 (0.90 to 1.01)	0.97 (0.92 to 1.03)
Patient global assessment	64.3 (24.0)	55.5 (24.3)	0.99 (0.98 to 0.99)	0.002	0.99 (0.97 to 1.00)	0.99 (0.97 to 1.00)
Fatigue	54.0 (26.6)	42.2 (26.4)	0.99 (0.98 to 0.99)	0.0005	0.98 (0.97 to 0.99)	0.98 (0.97 to 0.99)
Low income	48 (23.0)	26 (14.4)	0.53 (0.31 to 0.88)	0.02	0.53 (0.29 to 0.97)	0.49 (0.26 to 0.91)
Glucocorticoids (ever vs never exposed)	159 (71.6)	129 (65.8)	0.76 (0.50 to 1.15)	0.2	–	1.05 (0.62 to 1.79)
csDMARDs (ever vs never exposed)	205 (92.3)	169 (86.2)	0.52 (0.27 to 0.98)	0.04	–	0.55 (0.25 to 1.20)
bDMARDs (ever vs never exposed)	93 (41.9)	57 (29.1)	0.57 (0.38 to 0.85)	0.006	–	0.39 (0.23 to 0.67)
	BSL for AbsSDP					**BIT for AbsSDP**
	Univariate analysis				Multivariable analysis	Multivariable analysis
Variables	No AbsSDP (n=252)	AbsSDP (n=91)	OR for AbsSDP (95% CI)	P value	OR for AbsSDP (95% CI)	OR for AbsSDP (95% CI)
Mean total vSHS	1.8 (2.5)	5.9 (7.7)	0.82 (0.76 to 0.88)	<0.0001	0.82 (0.76 to 0.88)	0.82 (0.75 to 0.88)
CRP	18.1 (28.3)	25.3 (32.8)	0.99 (0.99 to 1.00)	0.04	0.99 (0.98 to 1.00)	0.99 (0.98 to 1.00)
ACPA positivity	99 (33.3)	71 (78.0)	0.18 (0.10 to 0.31)	<0.0001	0.14 (0.07 to 0.27)	0.22 (0.10 to 0.43)
TJC (/28)	10.8 (7.3)	8.7 (6.7)	1.05 (1.01 to 1.09)	0.01	1.04 (0.99 to 1.09)	1.04 (0.99 to 1.09)
Glucocorticoids (ever vs never exposed)	161 (69.1)	61 (73.5)	0.73 (0.40 to 1.29)	0.28	–	–
csDMARDs (ever vs never exposed)	196 (84.1)	81 (97.6)	0.14 (0.02 to 0.48)	0.02	–	0.22 (0.03 to 1.05)
bDMARDs (ever vs never exposed)	59 (25.3)	51 (61.5)	0.26 (0.15 to 0.45)	<0.0001	–	0.30 (0.16 to 0.56)

Data are n (%) or mean (SD).
Low income: <610 €/month.
AbsSDP, absence of structural damage progression; ACPA, anticitrullinated peptide antibody; bDMARD, biological disease-modifying antirheumatic drug; BIT, binary treatment model; BSL, baseline model; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score in 28 Joints; ESR, erythrocyte sedimentation rate; FavOut, favorable outcome; HAQ-DI, Health Assessment Questionnaire Disability Index; RF, rheumatoid factor; TJC, tender joint count; vSHS, Sharp/van der Heijde Score.

1050.3 and 1216.5 days, respectively. The most-prescribed bDMARDs were tumour necrosis factor inhibitors: 143 (34.2%) and 112 (32.7%) in the FavOut and AbsSDP groups.

Thus, 41 (9.8%) and 40 (11.7%) patients in the FavOut and AbsSDP groups were never exposed to DMARDs during the 10-year follow-up.

FavOut at 10 years

In total, 196 (46.9%) patients showed a FavOut at 10 years.

The multivariate BSL was built considering the following baseline prognostic factors: age at RA onset, DAS28-ESR, total mean vSHS, patient global assessment, fatigue, low income and HAQ-DI. Odds of FavOut were reduced with age at RA onset, fatigue and low income at baseline: OR 0.96 (95% CI 0.94 to 0.98), OR 0.98 (95% CI 0.97 to 0.99) and OR 0.53 (95% CI 0.29 to 0.97), respectively (table 2).

In the BIT, the same baseline characteristics as in the BSL were considered (table 2). On univariate analysis, FavOut was reduced with exposure to csDMARDs and bDMARDs during follow-up, and therefore these were integrated in the BIT, in addition to the previously mentioned baseline variables. Exposure to bDMARDs at any time of the follow-up remained significantly associated with reduced odds of FavOut: OR 0.39 (95% CI 0.23 to 0.67).

Finally, when modelling csDMARD and bDMARD exposure as WCE variables, exposure to both drug classes was significantly associated with FavOut on univariate

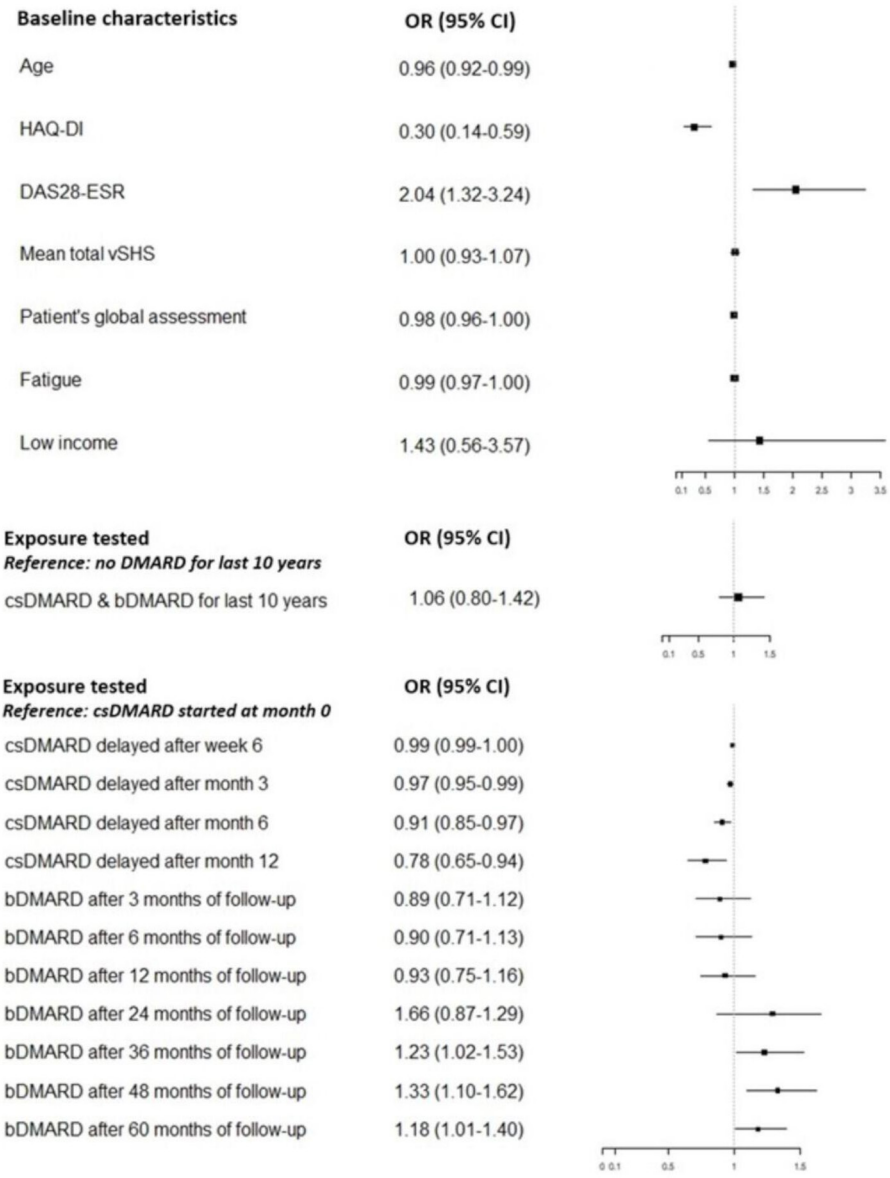


Figure 4 Results of the weighted cumulative exposure combined model for favourable outcome. bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28, Disease Activity Score in 28 Joints; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire Disability Index; vSHS, Sharp-van der Heijde Score.

analysis (online supplemental material 3) and therefore included in the final WCE combined model (figure 4). Thus, different profiles of drug exposures were compared (figure 1). In this WCE model, odds of FavOut were increased with early initiation of csDMARDs (as soon as inclusion in the ESPOIR cohort) as compared with initiation at 6 weeks or 3, 6 or 12 months after inclusion. Combined treatment with csDMARDs (initiated early) and bDMARDs (with different delays of bDMARD initiation) versus early initiated csDMARD monotherapy had no significant benefit for FavOut. The sensitivity analysis performed in patients having initiated a DMARD in the first year of follow-up (n=343) found similar results (online supplemental material 4).

The three models displayed good predictive performance, but the WCE model had the highest AUC versus the BSL and BIT: 0.80 (95% CI 0.74 to 0.87) (figure 5A).

AbsSDP at 10 years

Overall, 91 (26.5%) patients showed SDP at 10 years, with a mean progression in progressors of 34.4±22.8 points according to vSHS. Thus, AbsSDP was observed in 252 (73.5%) patients.

The multivariate BSL was built considering the following baseline prognostic factors: tender joint count, CRP level, CPA positivity and mean total vSHS. Odds of AbsSDP were reduced with ACPA positivity (OR 0.14, 95% CI 0.07 to 0.27) and mean total vSHS at baseline (OR 0.82, 95% CI 0.76 to 0.88) (table 2).

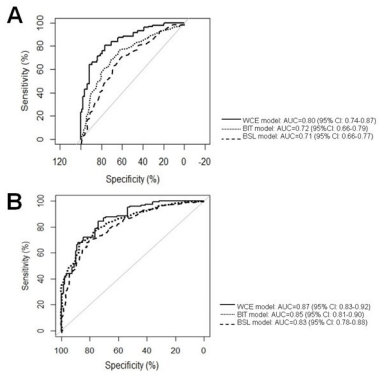


Figure 5 Receiver operating characteristic curve analysis of multivariate models. (A) Favourable outcome. (B) Absence of structural damage progression. AUC, area under the curve; BIT, binary treatment model; BSL, baseline model; WCE, weighted cumulative exposure.

In the BIT, the same baseline characteristics as in the BSL were considered. On univariate analysis, exposure to csDMARDs and bDMARDs during follow-up was significantly associated with AbsSDP and therefore was integrated in the BIT, in addition to the previously mentioned RA prognostic factors. Odds of AbsSDP were reduced with exposure to bDMARDs (OR 0.30, 95% CI 0.16 to 0.56) (table 2).

When modelling csDMARD and bDMARD exposure as WCE variables, these exposures were significantly associated with AbsSDP on univariate analysis (online supplemental material 5) and were therefore included in the final WCE combined model (figure 6). Thus, different profiles of drug exposures were compared (figure 1). Odds of AbsSDP were associated with early initiation of csDMARDs (as soon as inclusion in the ESPOIR cohort) as compared with initiation at 3, 6 or 12 months of follow-up. Additionally, combined treatment with csDMARDs (initiated early) and bDMARDs (with different delays of bDMARD initiation) versus early initiated csDMARDs monotherapy had no significant benefit for AbsSDP. The sensitivity analysis performed in patients having initiated a DMARD in the first year of follow-up (n=271) found similar results (online supplemental material 6).

The three models had good predictive performance, but the WCE combined model had the highest AUC versus the BSL and BIT (0.87, 95% CI 0.83 to 0.92) (figure 5B).

DISCUSSION

In this study, we built three predictive models for FavOut and AbsSDP after 10 years with RA. According to the results of the WCE models, which had the best predictive performance, FavOut and AbsSDP were positively associated with early csDMARD initiation as compared with a delay of 3, 6 or 12 months; thus, these findings favour a WoO in RA.

The ESPOIR cohort data were appropriate for this study: indeed, because this cohort featured follow-up of patients since the very beginning of the disease, the 10-year outcomes reflect the evolution of RA as observed in real-life settings. Moreover, given that the cohort protocol did not interfere in treatment, it provided medical data more representative of medical daily practice than randomised controlled trials.[11]

To our knowledge, this is the first study to assess the long-term impact of treatments (modelled as WCE variables) on 10-year outcomes in RA, taking into account RA prognostic factors. van Nies *et al*[7] studied the WoO in RA but in terms of short-term outcomes and without assessing the impact of treatment exposure. Louveau *et al*[20] studied the impact of drug exposure on RA outcomes but in terms of mid-term outcomes, with only a few patients receiving bDMARDs, and thus with lack of power. Niemantsverdriet *et al*[24] investigated the impact of early referral to a rheumatologist on long-term outcomes in ESPOIR but did not analyse the impact of early treatment initiation. A study based on the Norfolk Arthritis Register aimed to assess the association between early treatment and 20-year outcomes, but treatment exposure was assessed qualitatively: early exposure (≤6 months after symptom onset), late treatment (>6 months after symptom onset) and never exposed.[25]

Here, we confirm the interest of associating treatments and baseline characteristics as determinants of radiographic progression and FavOut at 10 years; indeed, in our study, models including treatment exposure (WCE combined model and BIT) had better predictive performance than models including baseline characteristics alone. The BIT revealed a potentially deleterious effect of DMARDs, which contradicts the findings of previous experimental and observational studies of the impact of DMARDs on RA outcomes.[26 27] In contrast, the WCE models revealed a beneficial effect of DMARDs. Thus, the results of the BIT are likely related to confounding by indication bias, not corrected by inappropriate modelling of the treatment exposure. In addition, modelling the treatment exposure as a dichotomous variable results in loss of information because it does not take into account the duration of drug exposure, the dosage and the timing of drug initiation.

With the WCE model, we compared various profiles of the association of csDMARD and bDMARD exposures. We focused on initiation of csDMARDs and bDMARDs at different times during the first 3 years of follow-up (and thus the disease course): indeed, in the ESPOIR cohort, half of the patients undergoing a biological therapy initiated a bDMARD in the first 3 years of follow-up.[28] According to previous studies, there is a WoO in the first months of the RA course[29 30]: joint damage occurs early in the disease and 90% of patients have radiological evidence of damage by the end of 2 years of symptoms.[31] As compared with delayed initiation, early csDMARD initiation (as soon as the inclusion visit) was associated with FavOut at 10 years and AbsSDP at 10 years; this

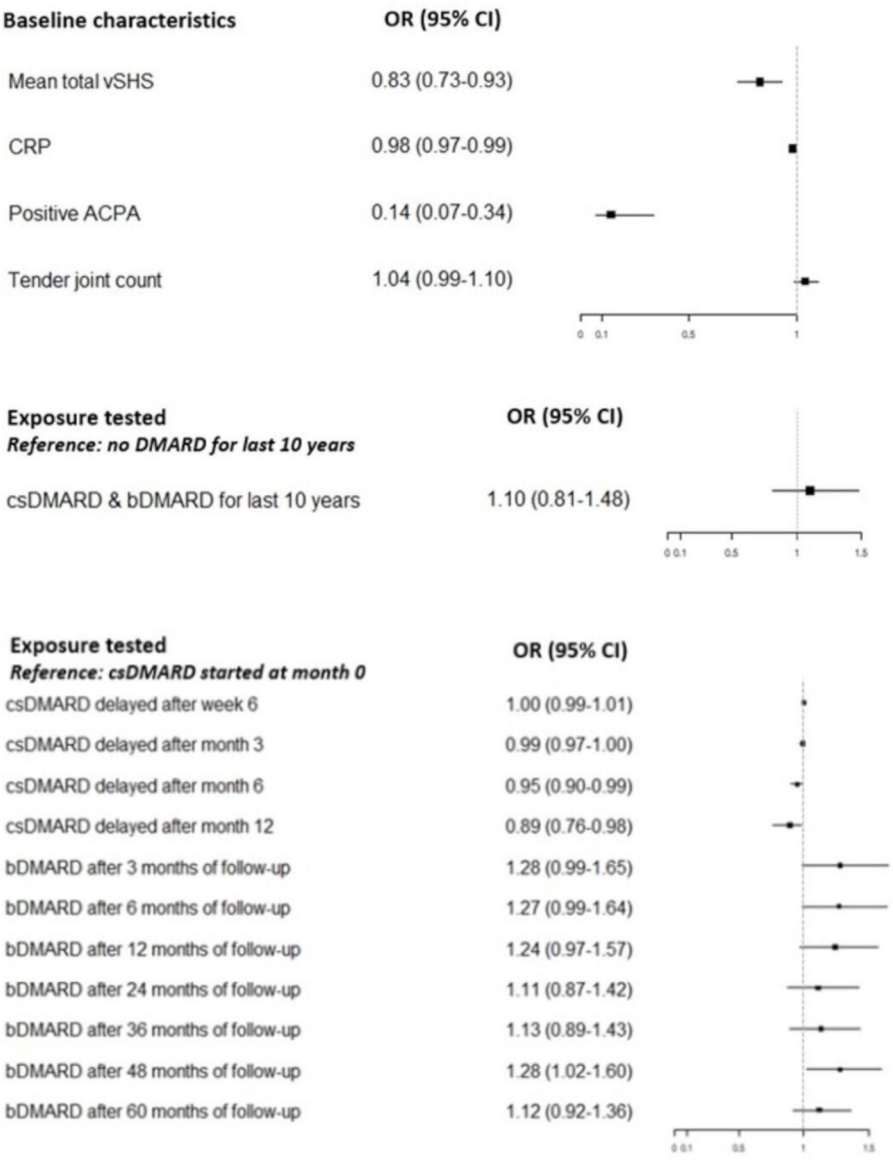


Figure 6 Results of the weighted cumulative exposure combined model for absence of structural damage progression. ACPA, anticitrullinated peptide antibody; bDMARD, biological disease-modifying antirheumatic drug; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; vSHS, Sharp-van der Heijde Score.

finding confirms the benefit of a WoO for csDMARDs. Previous studies of the ESPOIR cohort showed the interest of initiating a csDMARD in the first 3 months of the disease course but only for short-term outcomes (12 months).[32 33] Our findings indicate that this benefit is maintained over the long term, up to 10 years at least.

Also, as compared with early initiation of csDMARD therapy, initiation of a bDMARD along with a csDMARD in the first 3 years of follow-up was not significantly associated with 10-year outcomes. Therefore, there may be no 'lost opportunity' in initiating a bDMARD after a csDMARD as compared with using bDMARDs as first-line treatment. This point agrees with the current international recommendations.[5 6]

This work has several limitations: first, we investigated drugs with similar modes of action and did not study the individual effect of each csDMARD or bDMARD. This would have been interesting but was not possible in the present study, given that some of these treatments were prescribed in only a few patients, and including all these variables would have led to a great number of parameters with a relatively low number of patients and events. A larger sample size would have improved the modelling of each exposure. Furthermore, even if our final models included well-known baseline characteristics associated with RA outcomes, we did not adjust our analysis on time-varying confounding factors. Assessing the impact of disease activity, acute phase reactants or radiological scores at various times of the follow-up would have been interesting; however, the ESPOIR cohort design included data collection at fixed intervals (6, 12, 18 and 24 months, then annually), that is, without relation to disease flares

and eventual DMARD adjustment. Thus, RA characteristics at the time of DMARD changes were not available. More regular, flexible and exhaustive clinical data collection could have enabled time-varying modelling, using, for example, a generalised estimating equation model. However, to our knowledge, these models have never been used in association with WCE variables; additionally, more patients would have been needed.

In conclusion, the present study highlights the need to properly take into account treatment exposure, in terms of intensity and duration, to assess the potential long-term benefits in RA. It also reveals the long-term beneficial consequences associated with respect to a 3-month WoO when starting a DMARD in patients with early RA. The rapidity of treatment onset in early RA (ie, within the 3 months after diagnosis) is a major prognostic factor for patients with RA and confirms the paradigm considering RA as a medical emergency.

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Contributors Design of the study and redaction of the manuscript: JK, AL, DH and BF; inclusion of patients in the Etude et Suivi des Polyarthrites Indifférenciées Récentes cohort: BC, MD and BF; verification of the underlying data and statistical analysis: JK, AL and DH; critical review of the manuscript, had full access to all the data in the study and were responsible for submission for publication: all authors. Guarantor: BF

Competing interests JK: received a grant from the French Society of Rheumatology for the present study. BC: received honoraria from AbbVie, BMS, Gilead, Galapagos, Janssen, Lilly, Merck, Novartis, Pfizer and Roche-Chugai; and research grants from Novartis, Pfizer and Roche; is a member of the editorial board and editor-in-chief of *RMD Open*. MD: received honoraria from AbbVie, BMS, Gilead, Galapagos, Janssen, Lilly, Merck, Novartis, Pfizer and Roche-Chugai; and research grants from Novartis, Pfizer, Abbvie and Roche. AL and DH: no disclosure to declare. BF: received research grants from AbbVie, Lilly, MSD and Pfizer, and honoraria from AbbVie, Amgen, Biogen, BMS, Celgene, Janssen, Lilly, Medac, MSD, Mylan, NORDIC Pharma, Novartis, Pfizer, Roche, Sanofi-Aventis, SOBI and UCB.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information. The data underlying this article will be shared on reasonable request to the corresponding author. The study protocol, consent form, case report forms, available data list, all scientific projects, newsletters and some others documents are on the cohort Etude et Suivi des Polyarthrites Indifférenciées Récentes (ESPOIR) website (www.lacohorteespoir.fr). The first patient was included on 13 November 2002, and the estimated completion date is 1 June 2025. The anonymised raw data are stored by the ESPOIR coordination centre and are non-publicly available.

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